Docket No. PHUS-28

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent application of:
FAOUR, J. et al.

Serial No.: 09/770,901
Filed: January 26, 2001

Group Art Unit: 1617
Examiner: Shaojia A. Jiang

For: Pharmaceutical compositions containing A COX-II inhibitor and a muscle relaxant

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

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I HEREBY CERTIFY THAT THIS PAPER OR FEE IS BEING DEPOSITED WITH THE UNITED STATES POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE COMMISSIONER FOR PATENTS.

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SECOND SUPPLEMENTAL DECLARATION UNDER RULE 37 C.F.R §1.132

Further to the Office Action mailed April 23, 2003, and the Supplemental Declaration mailed September 17, 2002, the undersigned hereby declares as follows:

My name is Ethel C. Feleder. I reside in Luis Maria Campos 449, 2° A, Buenos Aires, Argentina.

I am knowledgeable in the area of Pharmaceutical Sciences and in particular in the area of the clinical evaluation of pharmaceutical formulations. My education, experience, publications and awards are summarized in my curriculum vitae, which has been previously submitted.

I am familiar with the subject matter of the invention disclosed and claimed in the above-identified patent application. In particular, I am familiar with conventional methods of analgesic therapy with individual drugs and with combinations of drugs.

With regard to the subject matter of claims 1-8, 40-45 and 49-54, I understand that the claims cover a pharmaceutical composition comprising a COX-II inhibitor and a muscle relaxant.

With regard to the subject matter of claims 10-38 and 46-48, I understand that the claims cover a pharmaceutical dosage form comprising a COX-II inhibitor and a muscle relaxant.

As a medical doctor, it is my belief that the claimed pharmaceutical compositions and dosage forms provide significant advantages over conventional analgesic compositions and dosage

forms used in pain therapy. In particular, the claimed pharmaceutical composition and dosage form provide an enhanced analgesic affect as compared to the administration of either agent alone AND as compared to the administration of an NSAID and a muscle relaxant. The exemplary formulation of rofecoxib and pridinol, the claimed composition and the claimed dosage form provide an unexpectedly improved analgesic effect over an equidose composition comprising diclofenac (an NSAID) and pridinol.

As previously declared, a side-by-side study to compare the analgesic effects of the claimed composition versus a prior art composition was conducted. The test employed was a writhing test conducted according to the method previously described by Siegmund et al. (*Proc. Soc. Exp. Biol. Med.* (1957), 95, 729-731). The method is well known in the art as a test for determining the analgesic effect of a drug or combination of drugs. The method and results were described in detail in the prior supplemental declaration.

In support of the prior supplemental declaration, this declaration is accompanied by a translation (Exhibits A & B) of a report containing the data of the side-by-side study conducted to compare the analgesic effects of the composition comprising rofecoxib and pridinol versus a prior art composition comprising diclofenac and pridinol.

Based upon the data enclosed herewith, the following results were obtained.

1. When administered alone and at the above-noted doses, neither diclofenac nor rofecoxib nor pridinol provided a statistically significant reduction in the number of contortions observed as compared to control (FIGS. 1-3). This means that the drugs were dosed at subtherapeutic levels considering that both drugs have been reported to produce analgesic effects in different animal models.
2. When diclofenac was administered in combination with pridinol, no statistically significant reduction in the number of contortions was observed as compared to control (FIG. 4). This means that pridinol did not enhance (either additively or synergistically) the analgesic efficacy of diclofenac at the doses tested.
3. When rofecoxib was administered in combination with pridinol, a statistically significant reduction in the number of contortions was observed as compared to control (FIG. 5). This means that pridinol synergistically enhanced the analgesic efficacy of rofecoxib at

the doses tested, sinc each agent alone did not provide an analgesic effect at the doses tested.

Therefore, it is truly unexpected that the combined administration of a COX-II inhibitor and a muscle relaxant provides an improved, additive or synergistic analgesic effect when administered to a subject as compared to the analgesic effect provided by the administration of either agent alone or as compared to the administration of an NSAID and a muscle relaxant.

I further declare that the statements made herein, to my knowledge, are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date: 23rd October 2003

Dr. Ethel C. Feleder, M.D., Ph.D.

EXHIBIT A

Table 1: Number of Controtions per 10 minutes for each mouse as a function of drug administered and dosage level.

Dose (mg/kg)	Contortions per 10 minutes in each mouse						Mean'	S.D.
0.0 (Normal saline)	14	17	20	24			18.8	4.3
0.32	28	22	23	16	24	22	22.5	3.9
0.64	14	19	30	23	16	28	21.7	6.5
1.28	21	13	21	22	28	11	19.3	6.3
2.56	13	29	13	25	11	19	18.3	7.3

Dicl fenac Sodium

Dose (mg/kg)	Contortions per 10 minutes in each mouse				Mean	S.D.	P value of contr.
0.0 (Normal saline)	14	17	20	24	18.8	4.3	
16	29	14	7	9	14.8	9.9	0.4568
32	13	11	16	3	10.8	5.6	0.5330
64	2	18	0	16	9.0	9.3	0.9275

R f c xib

Dose (mg/kg)	Contortions per 10 minutes in each mouse										Mean	S.D.	
0.0 (1% CMC)	32	31	36	14							28.3	9.7	
16	12	12	17	10	7	13	2	2	10	18	3	9.6	5.6	0.0004
32	18	15	18	20	7	3	31	10				15.3	8.7	0.0864
64	35	22	25	12	23	17	17	0				18.9	10.2	0.6597

EXHIBIT B

Tabl 2: C nt rtions per 10 minutes for the combination of diclofenac sodium and rofecoxib and pridinol.

Dicl fenac Plus Pridinol

Dose (mg/kg)	Contortions per 10 minutes in each mouse						Mean	S.D.
0.0 (Normal saline)	14	14	35	7	19		17.8	12.1
16	12	26	20	7	9	4	13.0	8.4
32	25	15	15	11	12	37	19.2	6.0
64	20	12	9	21	25	12	16.5	5.9

R f c xib Plus Pridinol

Dose (mg/kg)	Contortions per 10 minutes in each mouse												Mean	S.D.
0.0 (1% CMC)	33	43	44	56	37	32							40.8	8.9
16	33	7	20	28	13	7	21	13	13	28	2	7	16.0	9.9
32	28	37	25	29	15	16	28	10	20	29	28		24.1	7.9
64	18	29	13	29	11	20	23	6	25	16	13	2	17.1	8.6

Table 3: Tw tailed T-Test statistical analysis of the combination of diclofenac & pridinol versus rofecoxib & pridinol

Diclofenac Plus Pridinol

Dose (mg/kg)	P value from Control
0.0 (Normal saline)	
16	0.4208
32	0.8308
64	0.8054

R f coxib Plus Pridinol

Dos (mg/kg)	
0.0 (1% CMC)	
16	0.0001
32	0.0012
64	0.0001